

## Empirical Studies of Multi-National Research

**Summary:** This project aims to understand the perspective and experiences of research participants in developing countries regarding the benefits of clinical research and the informed consent process.

**Section:** Human Subjects Research—Unit on Multi-National Research

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**Background:** There has been much controversy over biomedical research in developing countries that is sponsored by developed countries. One of the major foci of criticism is around the informed consent process. It is claimed that potential research participants in developing countries cannot provide informed consent. They are poor, poorly educated, have limited access to health care services, and limited understanding of the nature of research. These handicaps make it impossible for them to understand the nature of the research being proposed and force them to enroll. As one commentator argued:

[I]t is difficult to avoid coercing subjects in most settings where clinical investigation in the developing world is conducted. African subjects with relatively little understanding of medical aspects of research participation, indisposed toward resisting the suggestions of Western doctors, perhaps operating under the mistaken notion that they are being treated, and possibly receiving some ancillary benefits from participation in the research, are very susceptible to coercion.

Another has claimed:

You can tell a person [in a poor developing country] that this is research, but they hear they have a chance to get [health] care or else refuse their only good chance at care. How can you put them in that position and then say they are giving informed consent?

In the view of many people, these views have been confirmed most prominently by a famous front-page story in the *New York Times*. The correspondent interviewed a woman from the Ivory Coast enrolled in a randomized trial of HIV medications who “still [did] not grasp—even after repeated questioning—what a placebo is or why she might have been given that instead of a real medicine.”

Beyond this single vivid anecdote what are the empirical data regarding the quality of informed consent in developing countries? Similarly, what are the data indicating that potential research participants are coerced or have no real choice but to enroll in clinical research? Interestingly, there are few empirical studies on informed consent or voluntariness in developing countries. More importantly, there has not been a comprehensive assessment of these data and comparison with the quality of informed consent in developed countries.

Another major criticism of clinical research in developing countries contends that this research is exploitative. It is claimed that the research provides benefits to people in developed countries while exposing people in developing countries to risks of research. Whatever the benefits of biomedical research in developed countries, the benefits to the participants in developing countries is minimal and not worth the risks. Furthermore, it is argued that in some cases the country is actually worse off than before the research, that the health care infrastructure, especially the trained staff, becomes focused on the research and the delivery of basic health care services deteriorates and is worse when the developed country researchers depart. Others counter that in fact there are substantial benefits from the research in developing countries sponsored by developed countries. These countries receive medical interventions they might not otherwise get; people obtain employment and training; they receive facilities and equipment. In addition, research brings an intangible hope of cures for otherwise devastating health problems to people in developing countries.

What do the people in developing countries where research is being conducted believe? Do they think research exploits them? What do they perceive to be the key

benefits of research—medical interventions, employment, equipment, and psychological hope? What do they think the key risks of research are—exploitation, bad reputation? Interestingly, there is not even one empirical study assessing the attitudes of people in developing countries toward research.

Finally, in the midst of all the controversies surrounding multi-national research, clinical researchers and IRBs must make decisions about research trials. They must interpret international guidelines, decide whether certain trials adhere to international guidelines, what information to provide in informed consent documents, etc. What do they think the requirements of Helsinki about best-proven therapy mean? How do they weigh the requirement of reasonable availability in considering a research study? What is their view about including rare but serious harms in informed consent documents? Again, there has not been any comprehensive assessment of the views of clinical researchers or IRBs throughout the world about the controversies in multi-national research.

**Objectives:**

- 1) To determine the quality of informed consent among research participants in developing countries.
- 2) To determine whether individuals in developing countries approached to enroll in clinical research are coerced or are free to refuse to participate.
- 3) To determine what people in developing countries—both research participants and non-participants—perceive to be the benefits or risks of having research activities in their countries.
- 4) To determine the views of clinical researchers and IRB members outside the United States on the controversies in multi-national research, especially regarding research in developing countries.

**Methodology:** The first step in this research was to conduct a thorough literature search on informed consent in developing and developed countries selecting studies that: 1) used quantitative methods; 2) surveyed participants or parents of participants in actual research studies; and 3) assessed at least one domain of comprehension, motivations, and voluntariness. In addition, other researchers working on informed consent and on multi-national research in developing countries were consulted to identify all empirical studies on informed consent. A comprehensive assessment was performed comparing the available data from developing and developed countries based on the methodology, the motivations, understanding, and voluntariness of research participants.

A second step was to identify a research study in a developing country, in this case the Rakai Project in Uganda, and assess the question of whether people are forced to participate in research by examining how many times people refuse to participate when offered the chance to enroll, once they enroll how frequently they

withdraw, and how frequently they refuse to participate in certain aspects of the research, such as providing blood or other samples.

A third step was to develop a survey instrument to assess informed consent among research participants in developing countries. This survey instrument would assess participants understanding of the research study focusing on their knowledge of the interventions, the risks, and alternatives. It would also assess their motivations for participating in research, whether they experienced any pressure to participate, and if they experienced pressure, from whom, and whether they felt they could refuse to participate or withdraw. Once a template survey instrument was developed, this instrument would be adapted to specific studies in developing countries. Initially, we attempted to conduct an assessment of a study of measles vaccines among HIV infected women in Malawi. We then tried to conduct an assessment of a malaria treatment study in Uganda, an HIV treatment study in Thailand, and a helminth treatment study among HIV infected individuals in Zambia.

We developed complementary survey instruments to assess the attitudes of researchers, IRB members, and research participants about various aspects of multinational research, including what should be included in an informed consent document, the interpretation of the Declaration of Helsinki's best proven method requirement and the CIOMS "reasonable availability" requirement. We used these three complimentary survey instruments to survey researchers, IRB members, and participants on the ESPRIT trial. ESPRIT is a randomized trial assessing whether Interleukin-2 (IL-2) improves survival among HIV patients treated with anti-retroviral therapies. The ESPRIT trial involves 4,000 participants in 22 countries, mostly developed countries, but also Thailand, Argentina, and Poland.

Finally, we developed a survey to assess how participants and other community members in developing countries perceive clinical research in their community. The survey assesses what benefits people perceive to come from hosting research. The survey inquires about how people perceive employment, payment for participating in research, added health services, etc. Similarly, the survey inquires about what people perceive to be the risks of hosting research from developed countries including risks of the research as well as community stigmatization. This survey is being conducted in conjunction with the Rakai Project and will interview people who have participated in their studies, community leaders, and district members who have never been approached to be in the research studies.

**Results:** The comprehensive literature review revealed 4 studies of informed consent from developing countries—Thailand, South Africa, The Gambia, and Bangladesh—and only 16 from developed countries. There are general methodological concerns about the studies in developing countries. All surveyed only women; they are small with sample sizes ranging from 33 to 137; and the focus has been on HIV and pediatric vaccines. In general, when tested, the comprehension of participants in developing countries was fairly good, except regarding randomization and placebo controlled

designs. For instance, in Thailand women were assessed regarding an HIV vaccine and 88% knew the risk of a false positive blood test. In The Gambia where children were enrolled in a pneumococcal vaccine study, 90% of the mothers knew the purpose of the vaccine and 50% could name at least one side effect. Only one study examined motivations for participating in research, showing that most participated to improve their health. The results regarding voluntariness are more varied. In Thailand, all participants knew they could refuse, while in The Gambia only 9% of participants said it “would have been hard to refuse” to participate. Conversely, in Bangladeshi study only 48% of women knew they could withdraw, and in the South African study 98% of the participants thought the hospital would not allow them to quit the study. These results were consistent with qualitative studies from Senegal and Chile.

Importantly, these results are similar to results found in studies of informed consent in developed countries. Understanding of the research purpose of the study was between 30% to nearly 100%; understanding of the design features of the study, especially randomization, was poor. In a Finnish study of tamoxifen, 77% of participants failed to understand randomization while 50% of US participants in a myocardial infarction study and 50% of Dutch parents in a study of NSAIDs for pediatric fever also failed to understand randomization. Similarly the ability of participants to name side effects of the interventions was comparable to participants in developing countries. The primary motivation cited by almost all participants in research was prospect of health improvement with altruism as second. Finally, in 6 of the 7 studies that evaluated the question of voluntariness, at least 20% of participants—and as many as 45% in one study—did not know that they could withdraw from the research study. Overall, review of the extant data suggest that the quality of informed consent in developing countries is comparable to that in developed countries and that both are less than the ideal. This review also suggests there is a paucity of high quality data and additional studies are needed, especially with larger sample sizes, involving men, and non-HIV diseases.

Second, using the Rakai Project’s STD Control for AIDS Prevention Trial, a randomized, community based trial of intensive STD control conducted between 1994 and 1999. All adults aged 15 to 59 residing in 10 clusters in Rakai district were eligible to enroll in the study. They were to be interviewed each year and contribute biological samples, including blood, vaginal swabs, and urine. Overall, 7.1% of eligible participants did not consent to participate in the research study, and 11.0% of eligible respondents who participated subsequently withdrew, that is refused to participate in future interviews. In addition, approximately a quarter of those who enrolled refused to provide blood samples, 12% refused to provide urine samples, and approximately 10% of the eligible women refused to provide vaginal swabs. These data are important because they suggest at significant proportion of eligible subjects feel they can refuse to participate in research, can withdraw from research, and/or refuse to provide biological samples. Such refusal suggests that coercion or pressure either from the research team, poverty, or lack of access to health care services is not inherent or a necessary part of clinical research in developing countries as suggested by many commentators.

Data from the ESPRIT surveys of IRB members, researchers, and participants is currently being collected. As of November 2002, we have completed surveys of 62 IRB chairs and completed surveys of 103 researchers. In person interviews with 141 ESPRIT participants in Thailand was completed in August 2002. The surveys have been back translated into English and entered in a database. The preliminary data analysis indicate that:

Knew they could withdraw from ESPRIT at any time	71%
Felt pressure to join ESPRIT from other people	15%
Knew that their blood would be stored for future research	85%
Knew how many days they would have to take IL-2	98%
Knew likelihood of IL-2 causing flu like symptoms	98%
Knew IL-2 was an experimental and not proven therapy	88%

The surveys of participants in the United States, England, Argentina and other countries are on going. As of November 2002 there were 133 completed surveys. Surveying will be complete when enrollment in ESPRIT is complete in January 2003.

**Future Directions:** A paper summarizing the comprehensive review of the quality of informed consent, and one reporting the Rakai Project data related to coercion have been submitted for publication.

We have developed a generic survey instrument to assess motivations, knowledge, and the quality of the informed consent process of both adult participants and parents of pediatric participants. These survey instruments contain 72 questions including open-ended responses.

In November, as part of the test and evaluation of one of the generic informed consent survey instruments, we initiated the survey of parents of children with malaria enrolled in randomized studies of three different anti-malaria treatments. This survey is being conducted at four sites in Uganda in conjunction with East African Network for Monitoring Antimalarial Treatment (EANMAT). Data collection from approximately 250 parents of pediatric participants should be completed by January 2003. This evaluation should provide a test of the survey instrument. It will also constitute the largest empirical assessment of the quality of informed consent in developing countries.

The generic survey instrument for research participants will also be used in conjunction with the University of Alabama, Birmingham and researchers in Lusaka, Zambia as a substudy of a randomized trial “to evaluate the impact of treatment of helminth infections on plasma HIV viral load.” This should provide additional data on the quality of informed consent in a developing country setting.

After these studies in Uganda and Zambia, we will make revisions to the survey instruments, and then place this survey instrument in the public domain. We plan to distribute this survey instrument to the African researchers that have attended our educational conferences have asked for such an instrument so they could conduct ethics sub-studies of their clinical research projects. In addition, we will work with the Pan-African Bioethics Initiative (PABIN), to distribute the survey instrument to their members. The objective is to develop a substantial body of data on the quality of informed consent using the same survey questions in different countries, with different research participants, in different types of clinical studies.

The study of how participants and community members in Rakai Uganda perceive the benefits and risks of research is just beginning. The survey is being pilot tested in December 2002 and we anticipate a 6-8 month data collection phase.

After completing several empirical studies of informed consent in developing countries, we plan to devise one or several interventions to improve informed consent. The precise nature of these interventions will depend upon the barriers to informed consent that we identify in our work. We would then plan to evaluate the interventions for their impact on informed consent.

## **Publications:**

Pace C, Grady C, Emanuel, E. The Quality of Informed Consent for Clinical Research: A Comparative Review of Empirical Data from Developing and Developed Countries. (submitted).